

# The effect of vaginal cream containing ginger in users of clotrimazole vaginal cream on vaginal candidiasis

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## ABSTRACT

Vulvovaginal candidiasis is one of the most common infections of the genital tract in women that causes many complications. Therefore, we examined the clinical effect of ginger cream along with clotrimazole compared to vaginal clotrimazole alone in this study. This double-blind clinical trial was conducted on 67 women admitted to the Gynecology Clinic of Hajar Hospital with vaginal candidiasis. The patients were divided randomly into two groups of 33 and 34 people. The diagnosis was made according to clinical symptoms, wet smear, and culture. Ginger-clotrimazole vaginal cream 1% and clotrimazole vaginal cream 1% were administered to groups 1 and 2, respectively, once a day for 7 days and therapeutic effects and symptoms were evaluated in readmission. Data analysis was performed using SPSS version 22, *t*-test and Chi-square. The mean value of variables itching ( $P > 0.05$ ), burning ( $P > 0.05$ ), and cheesy secretion ( $P < 0.05$ ) in users of ginger-clotrimazole was less than the other group after the treatment. Recurrence in clotrimazole group was 48.5% and in ginger-clotrimazole group 51.2% during the 1-month follow-up with no significant difference. Study results showed that cream containing ginger and clotrimazole 1% was more effective and may be more useful than the clotrimazole to treat vaginal candidiasis.

**Key words:** Clotrimazole, ginger, vaginal candidiasis

## INTRODUCTION

In the recent years, yeast of the genus *Candida*, as an opportunistic and nosocomial fungal pathogen, has been raised.<sup>[1]</sup> Preterm labor, urinary tract infection, and reduced quality of life and even life-threatening are other complications of vulvovaginal candidiasis. Besides that, infections associated with candidiasis impose high health-care costs on the health-care system.<sup>[1,2]</sup>

One of the drugs which have been taken into consideration to treat vulvovaginal candidiasis in the recent years is clotrimazole that is administered as suppository. However, the recent studies have shown that some *Candida* species, particularly *Candida albicans*, have become resistant to azoles with a change in their genetic structure that has caused the recurrence of vulvovaginal candidiasis. Furthermore, these drugs have various complications.<sup>[2,3]</sup> Therefore, the development of new drugs is very important. One of the plants whose therapeutic and prophylactic properties have long been considered in many diseases is *Zingiber officinale*.<sup>[4,5]</sup> Ginger is a tropical plant that occurs abundantly in India and Malaysia. Ginger genus includes about 85 species of

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aromatic plants which are distributed from East Asia to tropical areas of Australia.<sup>[6]</sup>

Due drug resistance and complication of chemical drugs and increasing popularity of medicinal herbs among the people, we conducted this study to determine the therapeutic effect of vaginal cream containing ginger and clotrimazole compared with clotrimazole vaginal cream on vaginal candidiasis.

## METHODOLOGY

### Extraction method

The dried *Z. officinale* was completely pulverized. Extraction was conducted by maceration.<sup>[4,5]</sup> To do this, ginger powder was mixed with boiled distilled water and kept with the same amount of ethanol 96% for 24 h *in vitro*. Then, filtration was carefully conducted by large and small filter papers and the solution concentrated in the rotary instrument and dried at 37°C. Then, cream 1% was prepared with clotrimazole vaginal cream base. To standardize the extraction, total phenolic, flavonoid, and flavonolic contents were measured.

### Measurement of total phenolic compounds

Total phenolic compounds were measured according to Folin–Ciocalteu colorimetric method in terms of gallic acid.<sup>[7,8]</sup> Standard solutions at concentrations of 12.5, 25, 50, 62.5, 100, and 125 ppm of gallic acid were prepared in methanol 60% solution. Then, 1.0 ml of each solution was transferred to test tube and 5.0 ml of a Folin–Ciocalteu 10% reagent solution was added to them. After 3–8 min, 4.0 ml of sodium carbonate 7.5% solution was added; then, the tubes were kept for 30 min at laboratory temperature, and optical density was measured by a spectrophotometer at 765-nm wavelength and accordingly, standard curve was plotted. Then, we dissolved 0.01 in 0.02 g of dried sample extract in methanol 60% until it reached a volume of 10 ml. Total phenolic content was determined according to Folin–Ciocalteu method, with the difference that 0.1 ml of the extract solution was added instead of the standard solution. We incorporated the amount of absorbance into the standard curve, and thus the extract's total phenolic content was obtained in mg/g gallic acid.

### Determining total flavonoids content

The aluminum chloride colorimetric method was used.<sup>[9]</sup> Rutin was used to plot the calibration curve. Ten mg of rutin was dissolved in 80% ethanol and diluted to 25, 50, and 100 µg/mL. The diluted standard solutions (0.5 mL) were independently mixed with 1.5 mL of 95% ethanol, 0.1 mL of 10% aluminum chloride, 0.1 mL of 1 M potassium acetate, and 2.8 mL of distilled water. After incubation for 30 min at room temperature, reaction mixture absorbance was measured at 415 nm wavelength. Ten percent aluminum chloride was replaced with an equal amount of distilled water in the blank. Similarly, 0.5 mL of ethanol extracts or

flavonoid standard solutions were reacted with aluminum chloride to measure flavonoid content.

### Investigating the effect of cream

This is a double-blind clinical trial which was conducted on women with vaginal candidiasis referring to the Gynecology Clinic of Hajar Hospital in 2015. The sample size in this study was determined 33 people in each group. Sixty-seven eligible women, enrolled at referral to the clinic, were randomly assigned to case and control groups in order of the enrollment. The first group which included 33 patients nightly used 1% clotrimazole vaginal cream (Raha Pharmaceutical Co.) with an applicator for 7 days.<sup>[10]</sup> The second group which included 34 patients nightly applied - ginger 1% clotrimazole vaginal cream 1% with an applicator for 7 days.

Inclusion criteria were being 25–35 years and married, having vaginal candidiasis symptoms according to interviews and observations and confirmed by the laboratory tests, and providing informed consent for participation in the study. Pregnancy, menstruation, abnormal uterine bleeding, acute vaginitis or vaginal trichomoniasis or fixed cervicitis with smear, certain diseases such as immune system dysfunction, diabetes, nephrotic syndrome, hypertension, heart disease, epilepsy, thyroid disorders and any malignancies or autoimmune diseases, use of Intrauterine Device for Birth Control and estrogen drugs, having more than one sexual partner, oral antifungal drug consumption within the previous 4 weeks and topical application over the past 2 weeks, use of antibiotics and corticosteroids during the previous 2 weeks and sensitivity to clotrimazole and ginger were considered the exclusion criteria. The groups were matched by age, level of education, and level of personal hygiene and preventive methods. After a history of the patients was taken, an interview-administered checklist was given to the patients in case of suspicious vaginal candidiasis. The clinical symptoms included vaginal cheesy secretions, vaginal erythema, itching of the vulva and vagina, vulva and vaginal irritation, dysuria, and painful sexual intercourse. In the checklist, vaginal itching, burning vulva and vaginal, dysuria, and cheesy secretions were divided into five categories of no, mild, moderate, severe, and very severe based on the severity, and each item was scored by a five-point scale. Examination of the patients was done by direct observation of vulva and vagina with speculum, and the secretions and vaginal erythema were investigated. Then the vaginal discharge of patients with primary diagnosis of vaginal candidiasis, confirmed by the gynecologist, was sampled to confirm the diagnosis. To identify the type of infection, one of the swabs was used to prepare microscopic slides and the other one to culture on fungi dextrose agar medium. Viewing germ string of fungi under a microscope using potassium hydroxide beside the examinations and positive clinical symptoms were considered to be diagnostic criteria of

vaginal candidiasis infection in the samples. To confirm the existence of *C. albicans* in culture, germ tube test was used. On readmission, the patients were examined again after 7 days and followed up for recurrence of symptoms by telephone calls 2 weeks after the end of treatment.

### Ethical considerations

The study was conducted after ethical approval and code (no. 26.1394) was provided by the institutional research department. The patients were enrolled with written informed consent. Before conducting the study, a pilot study to determine the sensitivity of the ginger-clotrimazole vaginal cream 1% was carried out that showed no complications in the patients.

### Statistical analysis

After collecting, data were analyzed by descriptive statistics, *t*-test, Mann-Whitney, and Chi-square tests in IBM Corp. Released 2013. Chicago, IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.).

## RESULTS

The study enrolled 67 married women that the mean age of 30.24 years and the mean marriage age of 21 years. The mean age, age of marriage, age at menarche, parity and previous deliveries, number of abortions, and number of infections are presented in Table 1.

There was no significant difference between the two groups in educational level, job, contraception methods, monthly income, and the frequency of intercourses per week [Table 2].

Before the treatment, the extent and severity of itching, burning, and cheesy secretions were not significantly different between the two groups. In ginger-clotrimazole group, the severity of symptoms was distributed almost uniformly, but the difference in burning and cheesy secretions was significant after the treatment [Table 3].

**Table 1: Comparison of mean age, age of menarche, and marriageable age in two groups under study**

Variable	Group (mean±SD)		P
	Clotrimazole	Ginger-clotrimazole	
Age	30.33±3.78	30.18±3.82	0.77
Age of marriage	21.27±3.32	21.79±3.78	0.55
Age of menarche	13.58±1.11	13.59±1.01	0.88
Parity	1.55±1.34	1.47±1.08	0.91
Previous deliveries	1.52±1.34	1.47±1.08	0.79
Number of abortions	0.03±0.17	0	0.31
Number of infections during the year	1.58±1.50	1.29±1.58	0.14

SD: Standard deviation

The two groups had no statistically significant difference in improvement of the itching ( $P = 0.42$ ). After the treatment, 15 people in clotrimazole group and 22 people in ginger-clotrimazole group did not report itching. Among the participants who had severe or very severe itching, five people in the first group and two people in the second group still reported moderate or severe itching after the treatment. Regarding burning, seven people in the first group and one in the second group complained of it. Moreover, there was not statistically significant difference between the two groups in recurrence of symptoms ( $P = 0.46$ ).

The recurrence rate of symptoms was 51.5% in clotrimazole and ginger group and 48.5% in clotrimazole group 1 month after the treatment, but the difference was not statistically significant ( $P = 0.46$ ).

According to laboratory studies on ginger, phenolic content was 116.46 mg/g, flavonoid content 42.49 mg/g, and flavonol content 26.6 mg/g.

## DISCUSSION

*Z. officinale* has been used for many human illnesses such as gastrointestinal diseases in different parts of the world since ancient times. The therapeutic properties of this plant are often associated with phenolic compounds and the antioxidant and anti-inflammatory properties of its root.<sup>[4,5]</sup> The most important therapeutic part of ginger is root, and different properties of the plant's root have been confirmed in addition to the contribution to treating gastrointestinal disorders, cold, fever, and arthritis. Antimicrobial and antifungal properties are other properties of this plant.<sup>[11]</sup> The results of this study showed that although mean scores of indicators such as itching, burning, and cheesy secretions in ginger and clotrimazole group was lower than those in clotrimazole group, the difference was statistically significant only in cheesy secretions. In line with the results of this study, it has been shown that ethanolic extract of *Z. officinale* at 1:5 concentration could be effective on oral *C. albicans*, and therefore, it can be considered therapy.<sup>[12]</sup>

A study to determine the antifungal effects of ginger rhizome showed that a protein in the plant can be used against numerous fungi.<sup>[13]</sup> A study that examined the antimicrobial properties of ginger extract 10% indicated that minimum inhibitory concentration was 2.5% in the ethanolic extract of ginger and inhibitory properties of this plant on bacteria were confirmed; as a result, this plant can be used as an antifungal compound.<sup>[14]</sup> In a review article that examined active compounds of ginger for the treatment of various diseases, the results showed that the rhizome of the plant has appropriate antibacterial and antifungal properties.<sup>[4]</sup> Studies show that substances such as [10]-gingerol and [12]-gingerol can play an important role in antimicrobial properties of ginger rhizome extract. Other

**Table 2: Comparison of educational level, job, contraception methods, monthly income, and the number of sex per week in two groups under study**

Variable	Group		P
	Clotrimazol, n (%)	Ginger-clotrimazol, n (%)	
Educational level			
Diploma	28 (84.8)	31 (91.2)	0.18
Associate degree	3 (9.1)	0	
BSc	2 (6.1)	3 (8.8)	
Job			
Homemaker	26 (78.8)	30 (88.2)	0.30
Self-employed	2 (6.1)	0	
Administrative	5 (15.2)	4 (11.8)	
Contraception			
Condoms	8 (24.2)	11 (32.4)	0.80
Permanent	2 (6.1)	1 (2.9)	
Natural	9 (27.3)	10 (29.4)	
Does not	14 (42.4)	12 (35.3)	
Income (US\$)			
<816	6 (18.2)	11 (32.4)	0.40
816-1632	22 (66.7)	19 (55.9)	
1632-2448	5 (15.2)	4 (11.8)	
Frequency of intercourses per week			
Less than once	4 (12.1)	3 (8.8)	0.29
One time	7 (21.2)	9 (26.5)	
Two times	6 (18.2)	1 (2.9)	
Three times	14 (42.4)	17 (50.0)	
Four times	2 (6.1)	4 (11.8)	

**Table 3: Comparison of disease symptoms before and after the treatment**

Variable	Group			
	Before treatment, frequency (%)		After treatment, frequency (%)	
	Clotrimazol	Ginger-Clotrimazol	Clotrimazol	Ginger-Clotrimazol
Itching				
No	3 (9.1)	2 (5.9)	15 (45.5)	22 (64.7)
Slight	10 (30.3)	11 (32.4)	13 (39.4)	10 (29.4)
Moderate	5 (15.2)	9 (26.5)	2 (6.1)	1 (2.9)
Severe	11 (33.3)	8 (23.5)	3 (9.1)	1 (2.9)
Most severe	4 (12.1)	4 (11.8)	0	0
P		0.76		0.42
Burning				
No	9 (27.3)	12 (35.3)	20 (60.6)	29 (85.3)
Slight	8 (24.2)	7 (20.6)	6 (18.2)	4 (11.8)
Moderate	8 (24.2)	5 (14.7)	4 (12.1)	0
Severe	6 (18.2)	6 (17.6)	3 (9.1)	1 (2.9)
Most severe	2 (6.1)	4 (11.8)	0	0
P		0.76		0.05*
Secretion				
No	6 (18.2)	14 (41.2)	20 (60.6)	30 (88.2)
Slight	14 (42.4)	11 (32.4)	12 (36.4)	4 (11.8)
Moderate	11 (33.3)	6 (17.6)	1 (3.0)	0
Severe	2 (6.1)	2 (5.9)	0	0
Most severe	0	1 (2.9)	0	0
P		0.19		0.01**

\*There is a significant difference between the groups in improvement of the burning so that  $P = 0.055$  for burning. This is not considered significant, \*\*Significant difference is seen between the two groups in improvement of the cheesy secretions so that  $P = 0.015$  for secretions which is considered a significant level

studies also confirm that the root of this plant has certain compounds such as<sup>[6-8]</sup> [10]-gingerol and [6]-gingerdiol, which is the reason for antimicrobial and antifungal properties of the plant. The percentage of these compounds is variable depending on the ginger race.<sup>[15]</sup> Terpenoids are one of the important compounds of ginger that have exhibited highly potent antifungal potential effects *in vitro*. These compounds inhibit the growth of this fungus *in vitro* through stopping various phases of cell division and destroying the integrity of *C. albicans* cells.<sup>[16]</sup>

Furthermore, recurrence of disease symptoms in this study did not show statistically significant difference between the two groups 1 month after the treatment. Clotrimazole may be effective in reducing the frequency of recurrence and ginger did not show substantially increasing therapeutic effect.

## CONCLUSION

Ginger and clotrimazole vaginal cream 1% is more effective than the clotrimazole vaginal cream 1% alone in the reduction of complaints and improvement of patients with vaginal candidiasis. This cream, as an herbal and natural medicine, may be a good alternative for people who cannot use azoles.

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## Conflicts of interest

There are no conflicts of interest.

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